REMARKS

Applicant submits this Amendment to indicate the insertion point for the Sequence Listing filed concurrently herewith. Application respectfully requests examination on the merits of this application.

Respectfully submitted,

By _____

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Date <u>July 5, 2001</u>

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Marked up replacementTables:

Table 3

```
                         FRI                      CDRI         FR2
                     1         2                3           4
                 12345678901234567890123  45678901234  567890123456789
AHM    (SEQ ID NO: 130)  DIVMTQSHKFMSTSVGDRVSITC  KASQDVNTAVA  WYQQKPGQSPKLLIY
HuSG I (SEQ ID NO: 131)  DIQMTQSPSSLSASVGDRVTITC               WYQQKPGKAPKLLIY
REI    (SEQ ID NO: 132)  DIQMTQSPSSLSASVGDRVTITC               WYQQKPGKAPKLLIY
RVLa   (SEQ ID NO: 133)  ----------------------   -----------  ---------------
RVLb   (SEQ ID NO: 134)  ----------------------   -----------  ---------------
```

```
                         CDR2         FR3
                     5            6         7         8
                     0123456      789012345678901234567890123456789012345678
AHM    (SEQ ID NO: 130)  SASNRYT      GVPDRITGSGSGTDFTFTISSVQAEDLALYYC
HuSG I (SEQ ID NO: 131)               GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
REI    (SEQ ID NO: 132)               GVPSRFSGSGSGTDFTFTISSLQPEDIATYYC
RVLa   (SEQ ID NO: 133)  -------      --------------------------------
RVLb   (SEQ ID NO: 134)  -------      --------------Y-----------------
```

```
                         CDR3         FR4
                     9            10
                     901234567    8901234567
AHM    (SEQ ID NO: 130)  QQHYSTPFT    FGSGTKLEIK
HuSG I (SEQ ID NO: 131)               FGQGTKVEIK
REI    (SEQ ID NO: 132)               FGQGTKVEIK
RVLa   (SEQ ID NO: 133)  ---------    ----------
RVLb   (SEQ ID NO: 134)  ---------    ----------
```

Table 4

```
                         FRI                                  CDR1    FR2
                     1         2         3                12345   4
                 123456789012345678901234567890   12345   67890123456789
AHM    (SEQ ID NO: 135)  QVQLQQSGAELARPGASVKLSCKASGYTFT  PYWMQ   WVKQRPGQGLEWIG
HuSGI  (SEQ ID NO: 136)  EVQLVQSGADVKKPGXSVXVSCKASGYTFS          WVRQAPGXGLDWVG
HG3    (SEQ ID NO: 137)  QVQLVQSGAEVKKPGASVKVSCKASGYTFN          WVRQAPGQGLEWMG
RVHa   (SEQ ID NO: 138)  ------------------------------T  -----   --------------
RVHb   (SEQ ID NO: 139)  ------------------------------T  -----   --------------
RVHc   (SEQ ID NO: 140)  ------------------------------T  -----   --------------
RVHd   (SEQ ID NO: 141)  ------------------------------T  -----   --------------
RVHe   (SEQ ID NO: 142)  ------------------------------T  -----   --------------
RVHf   (SEQ ID NO: 143)  ------------------------------T  -----   --------------
RVHg   (SEQ ID NO: 144)  ------------------------------T  -----   ----R---------
RVHh   (SEQ ID NO: 145)  ------------------------------T  -----   --------------
RVHi   (SEQ ID NO: 146)  ------------------------------T  -----   --------------
RVHj   (SEQ ID NO: 147)  ------------------------------T  -----   --------------
RVHk   (SEQ ID NO: 148)  ------------------------------T  -----   --------------
RVHl   (SEQ ID NO: 149)  ------------------------------T  -----   --------------
RVHm   (SEQ ID NO: 150)  ------------------------------T  -----   --------------
RVHn   (SEQ ID NO: 151)  ------------------------------T  -----   --------------
```

```
RVHo    (SEQ ID NO: 152)   ------------------------------T   -----   --------------
RVHp    (SEQ ID NO: 153)   ------------------------------T   -----   --------------
RVHq    (SEQ ID NO: 154)   ------------------------------T   -----   --------------
RVHr    (SEQ ID NO: 155)   ------------------------------T   -----   --------------
```

Table 5

```
                                   CDR2                      FR3
                                   5          6              7           8         9
                                   012A3456789012345         67890123456789012ABC345678901234
AHM     (SEQ ID NO: 156)           SIFPGDGDTRYSQKFKG         KATLTADKSSSTAYMQLSILAFEDSAVYYCAR
HuSGI   (SEQ ID NO: 157)                                     RVTXTXDXSXNTAYMELSSLRSEDTAVYYCAR
HG3     (SEQ ID NO: 158)                                     RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
RVHa    (SEQ ID NO: 159)           -----------------         -----A-------------------------
RVHb    (SEQ ID NO: 160)           -----------------         K----A-------------------------
RVHc    (SEQ ID NO: 161)           -----------------         -----A-K-----------------------
RVHd    (SEQ ID NO: 162)           -----------------         K----A-K-----------------------
RVHe    (SEQ ID NO: 163)           -----------------         -A-L-A-------------------------
RVHf    (SEQ ID NO: 164)           -----------------         -A-L-A---S--A------------------
RVHg    (SEQ ID NO: 165)           -----------------         -----A-------------------------
RVHh    (SEQ ID NO: 166)           -----------------         K----A---S--A------------------
RVHi    (SEQ ID NO: 167)           -----------------         K----A---S--A-------AF----------
RVHj    (SEQ ID NO: 168)           -----------------         KA-L-A---S--A------------------
RVHk    (SEQ ID NO: 169)           -----------------         K----A---S==A--Q---------------
RVHl    (SEQ ID NO: 170)           -----------------         K----A---S--A--Q--l------------
RVHm    (SEQ ID NO: 171)           -----------------         K----A---S--A--Q--l-----S------
RVHn    (SEQ ID NO: 172)           -----------------         K----A---S--A----l-------------
RVHo    (SEQ ID NO: 173)           -----------------         K----A---S--A----------S-------
RVHp    (SEQ ID NO: 174)           -----------------         -----A------A------------------
RVHq    (SEQ ID NO: 175)           -----------------         -----A---S---------------------
RVHr    (SEQ ID NO: 176)           -----------------         -----A-K----A------------------
```

Table 6

```
                                   CDR3               FR4
                                   10                 11
                                   57890ABJK12        34567890123
AHM     (SEQ ID NO: 177)           GLRRGGYYFDY        WGQGTTLTVSS
HuSGI   (SEQ ID NO: 178)           -----------        WGQGTLVTVSS
HG3     (SEQ ID NO: 179)           -----------        WGQGTTVTVSS
RVHa    (SEQ ID NO: 180)           -----------        -----------
RVHb    (SEQ ID NO: 181)           -----------        -----------
RVHc    (SEQ ID NO: 182)           -----------        -----------
RVHd    (SEQ ID NO: 183)           -----------        -----------
RVHe    (SEQ ID NO: 184)           -----------        -----------
RVHf    (SEQ ID NO: 185)           -----------        -----------
RVHg    (SEQ ID NO: 186)           -----------        -----------
RVHh    (SEQ ID NO: 187)           -----------        -----------
RVHi    (SEQ ID NO: 188)           -----------        -----------
RVHj    (SEQ ID NO: 189)           -----------        -----------
RVHk    (SEQ ID NO: 190)           -----------        -----------
RVHl    (SEQ ID NO: 191)           -----------        -----------
RVHm    (SEQ ID NO: 192)           -----------        -----------
RVHn    (SEQ ID NO: 193)           -----------        -----------
RVHo    (SEQ ID NO: 194)           -----------        -----------
RVHp    (SEQ ID NO: 195)           -----------        -----------
RVHq    (SEQ ID NO: 196)           -----------        -----------
RVHr    (SEQ ID NO: 197)           -----------        -----------
```

Design of V region of Natural Humanized Antibody

A) L chain

	FRI	CDR1	FR2	CDR2
	1 2	3	4 5	5
	1234567890123456789 0123	4567890123 4	5678901234567 89	0123456
HM1.24(SEQ ID NO: 130)	DIVMTQSHKFMSTSVGDRVSITC	KASQDVNTAVA	WYQQKPGQSPKLLIY	SASNRYT
HuSG I(SEQ ID NO: 131)	DIQMTQSPSSLSASVGDRVTITC		WYQQKPGKAPKLLIY	
REI (SEQ ID NO: 132)	DIQMTQSPSSLSASVGDRVTITC		WYQQKPGKAPKLLIY	
Primary design (RVLa	(SEQ ID NO: 133)			
Secondary design (SEQ ID NO: 133)	---------------------	----------	---------------	-------

	FR3	CDRI	FR2
	6 7 8	9	10
	78901234567890123456789012345678	901234567VA	8901234567
HM1.24(SEQ ID NO: 130)	GVPDRITGSGSGTDFTFTISSVQAEDLALYYC	QQHYSTPFT	FGSGTKLEIK
HuSG I(SEQ ID NO: 131)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC		FGQGTKVEIK
REI (SEQ ID NO: 132)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC		FGQGTKVEIK
Primary design (RVLa (SEQ ID NO: 133)			
Secondary design (SEQ ID NO: 133)	--------------------------------	----------	----------

Design of V region of Natural Humanized Antibody

B) H chain

	FR1		CDR1	FR2	CDR2
	1 2 3			4	5 6
	12345678901234567890123456789 0		12345	6789012345 6789	0123456789
HM1.24 (SEQ ID NO: 198)	QVQLQQSGAELARPGASVKLSCKASGYTFT		PYWMQ	WVKQRPGQGLEWIG	SIFPGDGDTRYSQKFKG
HuSG I (SEQ ID NO: 199)	EVQLVQSGADVKKPGXSVXVSCKASGYTFS			WVRQAPGXGLDWVG	
HG3 (SEQ ID NO: 200)	QVQLVQSGAEVKKPGASVKVSCKASGYTFN			WVRQAPGQGLEWMG	
Primary design (RVHr (SEQ ID NO: 201)	--------------------------T		-----	--------------	
Secondary design (2NDrvh) (SEQ ID NO: 202)	--------------------------T		-----		

	FR3		CDR3	FR2
	7 8 9		10	11
	67890123456789012ABC34567890123 4		57890ABJK12	34567890123
HM1.24 (SEQ ID NO: 198)	KATLTADKSSSTAYMQLSILAFEDSAVYYCAR		GLRRGGYYFDY	WGQGTTLTVSS
HuSG I (SEQ ID NO: 199)				
HG3/JH6 (SEQ ID NO: 200)	RVTXTXDXSXNTAYMELSSLRSEDTAVYYCAR			WGQGTTVTVSS

```
                           RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR----------------------WGQGTTVTVSS
Primary design (RVLa/Hr)   ----A-K----A--------------------------------------------------------
Secondary design (2nd RVH) ---I-A-K----A--------------------------------------------------------
```

Marked up page 74 line 23.

FR3 of primary design antibody (SEQ ID NO: 203)